UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/430,735	10/29/1999	NNOCHIRI N. EKWURIBE	4012-113-DIV	7685

7590 05/28/2003

J. MICHAEL STRICKLAND
MYERS BIGEL SIBLEY & SAJOVEC
POST OFFICE BOX 37428
RALEIGH, NC 27627

EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	20

DATE MAILED: 05/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/430,735	Ekwuribe et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26-35, 46-50, 61-63, 70, 71, and 73-97* is/are pending in the application.

4a) Of the above, claim(s) *26-35, 50, 61-63, 84, 86-93, and 95-97* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *46-49, 70, 71, 73-83, 85, and 94* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2,3,17*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 26-35, 46-50, 61-63, 70-71 and 73-97 are currently pending.

Claims 46-49, 70-71, 73-83 , 85 and 94 are under consideration.

Claims 26-35, 50, 61-63, 84, 86-93 and 95-97 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restriction

1. Applicant's election without traverse of Group II (claims 46-52) without traverse in Paper No. 6 is acknowledged. Claims 51-52 were subsequently canceled by applicant. New claims 70, 71 and 73-97 subsequently added read on the elected invention.

2. Claims 26-35 and 61-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (and/or being drawn to canceled embodiments as in claims 61-63).

3. Applicant's election without traverse of Met-Enk (Lys)$(PEG_4)(CH2)_{13}CH_3$ (E.g. Lys modified Met-Enk with hydrophilic PEG and hydrophobic alkyl) which reads on claims 46-49, 70-71, 73-83 , 85 and 94 is acknowledged.

4. Claims 50, 84, 86-93 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (and/or being drawn to canceled embodiments as in claims 61-63).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 46-49, 70-71, 73-83 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagi et al. US Pat. No. 5,061,691 (10/91) and Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier).

Yagi et al. teach the induction of analgesia by opioids (e.g endorphins/enkephalins) and the making of analogs of the peptide opioids Met- and Leu-enkephalins in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation; ability to pass thru blood-brain barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

The Yagi et al. reference teaching differs from the presently claimed invention which achieves analgesic therapy (e.g enteral/parenteral administration) of opioids (e.g. especially peptide opioids Met- and Leu-enkephalins) by conjugating the opioids (especially enkephalins) with a polymer which comprises lipophilic and hydrophilic moieties.

However, Ekwuribe teaches the stabilization of "therapeutic agents" (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties. E.g. see abstract; col 1-4 (e.g. stabilization). Opioids, especially peptidic opioids such as endorphins and enkephalins are preferred "therapeutic agents". See Abstract; col. 8 (lines 40-50); patent claims (especially claims 37-44). Therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as "other modes of physiological administration" (E.g. see col. 12, especially lines 5-10; col. 13, especially lines 45-55; col. 24-col. 24) including opthalmic, topical, bronchial, rectal, iv, subcutaneous, intrathecal etc (e.g. see col. 25-26). See also patent claims 35-44.

One of ordinary skill in the art would have been motivated to conjugate opioids (e.g. especially peptide opioids Met- and Leu-enkephalins and analogs thereof) as disclosed in Yagi et al. in the manner of Ekuwuribe to achieve an analgesic composition overcoming the *in vivo* obstacles recited in the Yagi reference.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to achieve opioid (e.g. enkephalin) analgesic therapy by modifying the

opioid with polymers comprising lipophilic and hydrophobic moieties as taught by Ekwuribe in order to obtain "stable therapeutic agents" for in vivo parenteral/enteral delivery.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekuwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

7. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagi et al. US Pat. No. 5,061,691 (10/91) and Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) as applied to claims 46-49, 70-71, 73-83 , 85 above, and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95).

The combined obviousness teaching of the Yagi and Ekwuribe patent references as discussed in the above rejection is hereby incorporated by reference in its entirety.

The combined teaching of Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon

amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 46-47, 70-71 and 73-82 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,309,633 (10/01) and Yagi et al. US Pat. No. 5,061,691 (10/91). Although the conflicting

claims are not identical, they are not patentably distinct from each other because the patent claims teaches conjugates and pharmaceutical compositions and the administration thereof which comprise a drug oligomer complex in which the oligomer comprises a hydrophilic portion (E.g. PEG) and a hydrophobic portion (e.g. alkyl chain) in which the claimed drug can be selected from a group of preferred drugs which include opioids (e.g. see claim 34 which includes dynorphins, endorphins and enkaphilins) the selection of which would have been obvious since these represent most preferred (e.g. claimed) drug embodiments. The analgesic therapeutic use of the patented therapeutic compositions would have been obvious to one of ordinary skill in the art at the time of applicant's invention upon *in vivo* delivery as taught by the Yagi et al. reference..

10. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,309,633 (10/01)and Yagi et al. US Pat. No. 5,061,691 (10/91). in view of Ekuwuribe US Pat. No. 5,681,811 alone and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95).

The combined '633 patent and Yagi patent obviousness teaching of the these reference recited above is hereby incorporated by reference in its entirety.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

The combined teaching of patent '633, Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

11. Claims 46-49, 70-71, 73-83 and 85 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-44 of Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Yagi et al. US Pat. No. 5,061,691 (10/91).

The Ekwuribe patent claims teach the stabilization of "therapeutic agents" (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties; with opioids, especially peptidic opioids such as endorphins and enkephalins being preferred "therapeutic agents". See e.g. patent claims (especially claims 37-44). The Claimed therapeutic

administration includes administration to humans via enteral (e.g. oral), parenteral, as well as "other modes of physiological administration" (E.g. see col. 12, especially lines 5-10; col. 13, especially lines 45-55; col. 24-col. 24) including ophthalmic, topical, bronchial, rectal, iv, subcutaneous, intrathecal etc (e.g. see col. 25-26). See also patent claims 35-44.
The analgesic therapeutic use of the patented therapeutic compositions would have been obvious to one of ordinary skill in the art at the time of applicant's invention upon *in vivo* delivery as taught by the Yagi et al. reference which teaches the induction of analgesia by opioids (e.g endorphins/enkephalins) and the making of analogs of the peptide opioids Met- and Leu-enkephalins in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation; ability to pass thru blood-brain barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described

therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moeity and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

12. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Yagi et al. US Pat. No. 5,061,691 (10/91) as applied to claims 46-49, 70-71, 73-83 , 85 above, and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95).

The combined obviousness teaching of the Yagi and Ekwuribe patent claims as discussed in the above rejection is hereby incorporated by reference in its entirety.

The combined teaching of Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingy, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for cabamate PEG attachment.

13. Claims 46-49, 70-71, 73-83 and 85 are rejected under the judicially created doctrine of provisional obviousness-type double patenting as being unpatentable over the claims (e.g. claims 46-52) of Ekwuribe et al. 09/429,798.

The Ekwuribe claims teach the analgesic administration of "therapeutic agents" (E.g. drug oligomer conjugates by conjugating with a polymer which comprises lipophilic and hydrophilic moieties; with opioids, especially peptidic opioids such as endorphins and enkephalins being preferred. See e.g. the claims (especially claims 46-52). The Claimed

therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as "other modes of physiological administration" (E.g. see specification).

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moieity) the same is rendered obvious by Ekwuribe. Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in (e.g. the drug is attached through a carbamate linkage adjacent to the PEG region of the polymer with the point of attachment of the carbamate bond between the polymers preferably is the amine function)

14. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekwuribe et al. 09/429,798. as applied to claims 46-49, 70-71, 73-83 , 85 above, and further in view of Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95).

The provisional obviousness teaching of the Ekwuribe patent application claims as discussed in the above rejection is hereby incorporated by reference in its entirety.

The Ekwuribe claims differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

The Ekwuribe patent '811 teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (cojugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekuwuribe '811 further teaches the ability to vary the position and number of hydrophilic/lipophilic moeities to achieve optimization. E.g. see col. 14, lines 50-60. Additionally, the Ekwuribe '811 patent specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14.

In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingy, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) to contain PEG-alkyl conjugates as disclosed in the pending claims of 09/429,798 to attach (via a carbamate bond) by use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of

the Ekwuribe application and patent teaching of using amino groups for cabamate PEG attachment.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)

May 27, 2003

BENNETT CELSA
PRIMARY EXAMINER